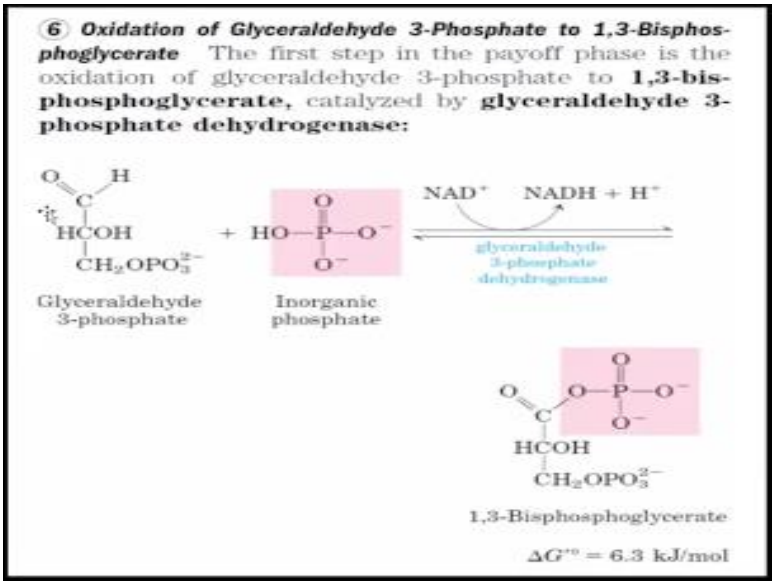
Introduction to Biomolecules
Prof. K. Subramaniam
Department of Biotechnology
Indian Institute of Technology-Madras

Lecture - 19
Glycolysis (Part 2/2)

(Refer Slide Time: 00:14)



So let us continue glycolysis that we discussed last Tuesday. So we stopped at the step after you know the hexose is cleaved into 2 trioses and then we saw dihydroxyacetone phosphate isomerasing into glyceraldehyde 3-phosphate. So today we will continue from glyceraldehyde 3-phosphate but at the end we will have an overview of all the 10 steps that form the glycolysis.

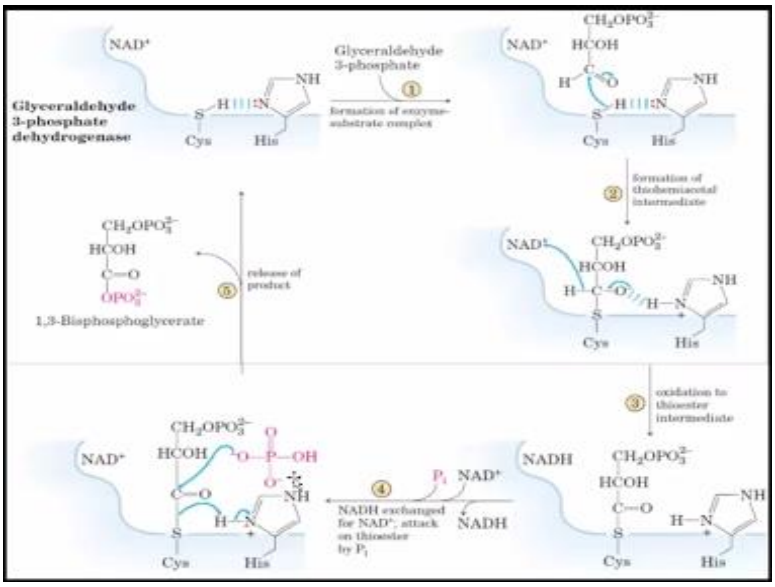
So oxidation of glyceraldehyde 3-phosphate is essentially this aldehyde group you know shown here on the left top is getting oxidized into a carboxylic acid group and the energy is conserved in making a phosphate mixed anhydride bond with a inorganic phosphate, that is one. And second part of that oxidation energy in terms of the electron transfer is used to reduce NAD to produce NADH, okay.

This pair is the hydride version of electron transfer. So two electrons and protons or one proton goes into the medium. So this is the first step of energy yielding phase of glycolysis. The steps we saw the previous ones like glucose to glucose 6-phosphate and then fructose 6-phosphate to fructose 1,6-phosphate.

So those are preparative steps where the bonds are energized like the poor leaving groups are replaced with the good leaving group, in this case phosphate. So those steps are called the preparative phase. So now, this is the first step where you will see energy yielding. So energy yielding in the sense here the electrons are transferred to reduce NAD, so that is one.

And this NADH if it enters into electron transport chain in mitochondria will approximately yield three electrons per NADH and here you have two glyceraldehyde 3-phosphate coming from a single glucose molecule. So as a result, you will get two NADH and therefore six ATP, so that possibility exists, okay. So temporarily it is conserved here.

(Refer Slide Time: 02:58)



And so let us look at its reaction mechanism. So this involves, so this is the active side of the enzyme where you have the oxidized NAD bound and then you have you know this non-covalent interaction between the sulfhydryls hydrogen and this electron rich nitrogen forming an interaction here. So this is the active site structure. So the first step is this hemiacetal, but there is a thiohemiacetal.

So this is an alcohol group, this is an aldehyde. Remember we learnt about how a ring structure of glucose forms. The aldehyde of the hexose forms an intramolecular hemiacetal with one of the alcohol groups which is the OH groups available in the in glucose molecule.

Very similarly, here the aldehyde of this carbohydrate, triose, instead of an intramolecular, like this would be an intramolecular alcohol group, this OH here, instead it is with an intermolecular and instead of alcohol this is thioalcohol forms a thiohemiacetal therefore, okay. So say again you can see this carbonyl group, this carbon will have partial positive charge and as a result, it is you know susceptible for nucleophilic substitution reactions.

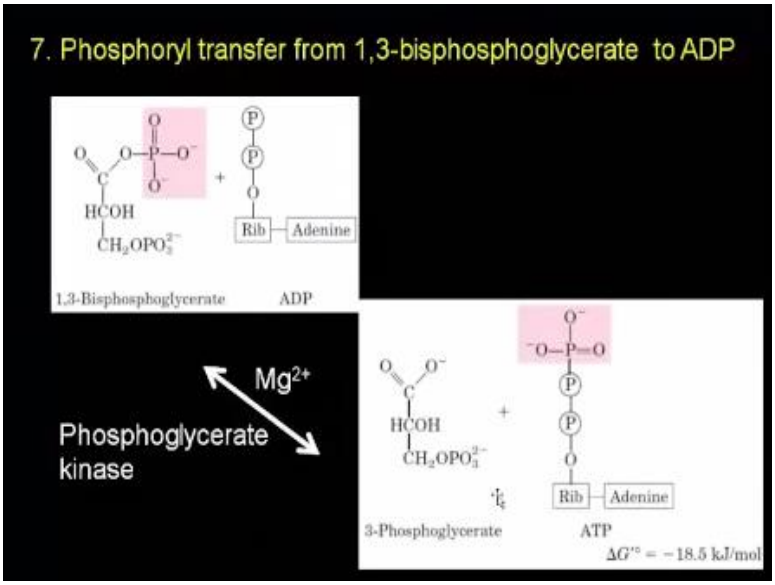
And that is how you get this thiohemiacetal. And that again undergoes oxidation to thioester form. So this is a thioester. This is no longer an alcohol group. Instead it is an acyl group and that is facilitated by the transfer of electrons from this to this NAD plus and that is how NAD gets reduced. And this transfer leads to the formation of this ester bond, this carbonate group.

And subsequently the reduced NADH is replaced by an NAD and so the original state returns. And phosphorolytic cleavage and instead of hydrolytic where it is water here it is inorganic phosphate and so there again you know this partial positive charge in this carbonyl makes that readily possible.

And that this also aided by this general base catalysis possible by this imidazole nitrogen of the histidine chain and that releases the product which is 1,3-bisphosphoglycerate. So essentially this thiohemiacetal oxidize to thioester, it gets phosphorolysed, okay instead of hydrolysis. So it is exchanged with this. So you have a mixed anhydride, carboxylic acid and then the inorganic phosphate.

So you end up getting two phosphates, okay. So this bond you know conserves the energy made available by the oxidation of the original aldehyde group to the final carboxylic acid group, okay. So this is a high energy phosphate, the one shown here this carbon phosphate bond. So this 1,3-bisphosphoglycerate is formed. So here you have net gain of two electrons per glyceraldehyde. So four electrons per glucose conserved in the form of reduced NADH.

(Refer Slide Time: 07:09)



And in the next step, which is the enzyme name is for the reverse reaction 3-phosphoglycerate gets phosphorylated to 1,3-bisphosphoglycerate. So the enzyme name comes from that phosphoglycerate kinase. But in glycolysis sequence this 1,3-phosphoglycerate that one of the high energy phosphate bond that is transferred by making an ATP molecule, okay. So here ADP gets phosphorylated forming the ATP.

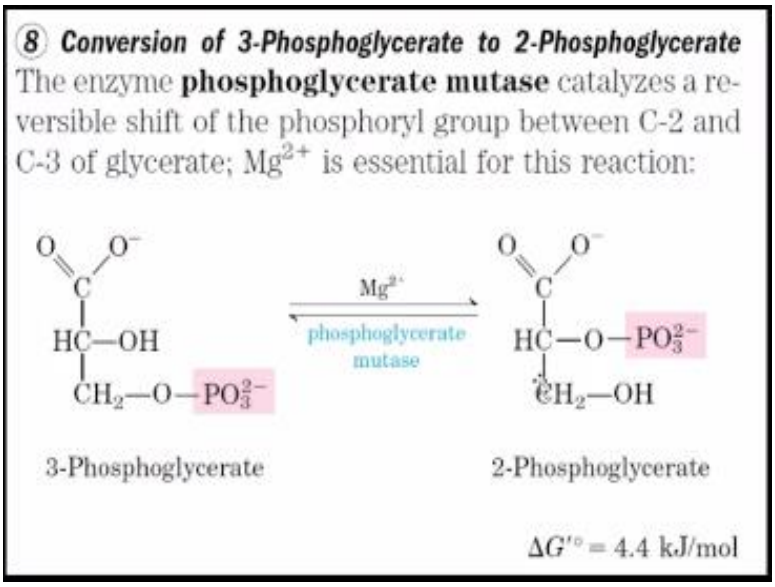
And the high energy bond here is now transferred to the formation of ATP. So this kind of a generation of an ATP molecule is usually called substrate level phosphorylation. Meaning from a substrate of this enzyme, you have the phosphate group transferred to make ATP.

This is in contrast to the oxidative phosphorylation based ATP formation in mitochondria, where the oxygen sorry electron transfer from one electron donor to another electron acceptor leads to the formation of a proton gradient. And then that proton gradient is used to make ATP. So that is called oxidative phosphorylation. To distinguish from that we call these kind of ATP formations as substrate level phosphorylation.

So this is the first substrate level phosphorylation you are encountering in glycolysis. So there is one more step later where we will see substrate level phosphorylation happening. So here this is the first step in glycolysis where you will see ATP formation. So here for one of the trioses you end up making one ATP. So per glucose you have generated two ATPs.

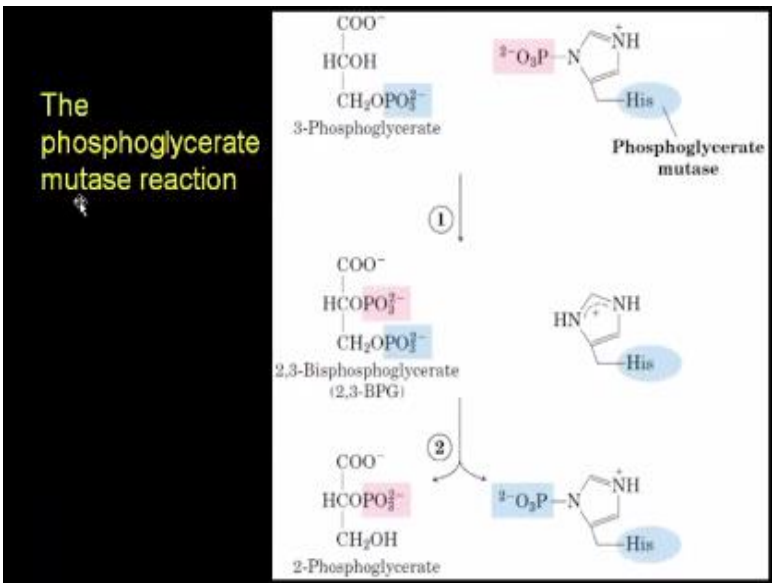
So this you know balances that two ATPs used in making glucose 6-phosphate and then the fructose 1,6 phosphate. So right now, in terms of ATP net gain is zero. The only thing is four electrons we abstracted have gone into making NADH. So NAD plus has been reduced. So that is the one gain.

(Refer Slide Time: 09:41)



And the next step is simply an isomerization where this ester is you know rearranged to the second carbon by mutase, phosphoglycerate mutase that converts 3-phosphoglycerate to 2-phosphoglycerate, which is very important for the progression of glycolysis because the next step involves a reaction that will generate another energy rich molecule.

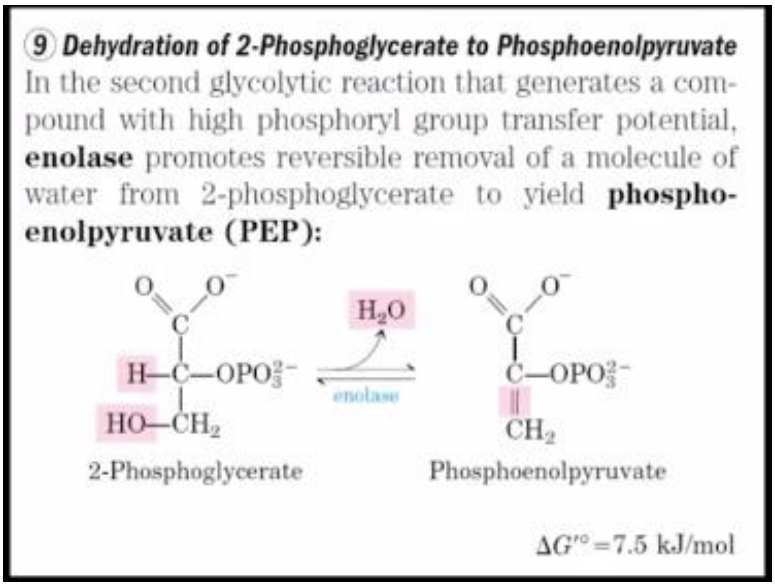
(Refer Slide Time: 10:16)



So this are the enzyme active site, happens in this manner. The first thing is actually a phosphoester bond with the second carbon with an enzyme that is already phosphorylated. This histidine imidazole side chain is phosphorylated, that donates the phosphate group making the 2,3-bisphosphoglycerate. And from this you have the original, the third carbon phosphate transferred to the enzyme so regenerating the enzyme's active site.

So this is an important intermediate, a small quantity, but it is crucial to make the reaction continuously proceed. So this 2,3 BPG is an important molecule in the glycolytic regulation. So this is how the mutase makes the 2-phosphoglycerate.

(Refer Slide Time: 11:16)

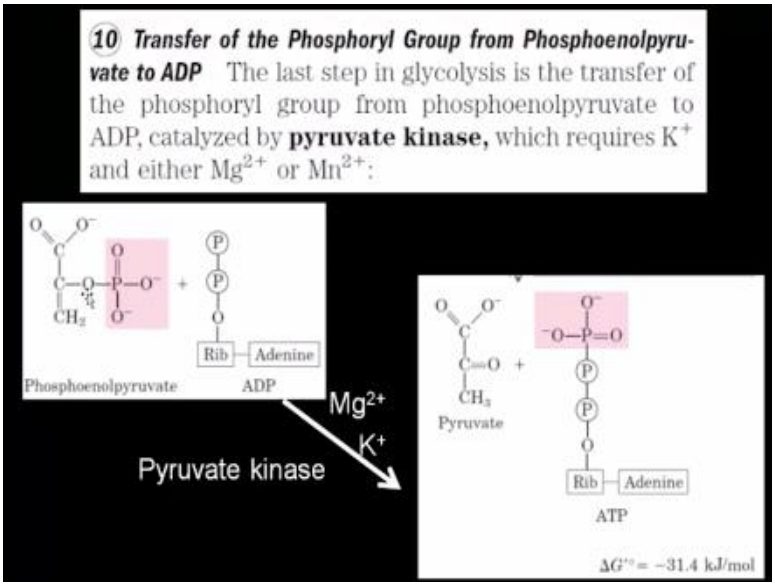


And the next step, so this is a 2-phosphoglycerate and this is redrawn from this to make it easy for us to understand how the dehydration happens leading to the formation of an enol structure. So this is catalyzed by enolase. This forms phophoenolpyruvate. And this is a high energy compound.

When we were talking about how ATP is a high energy compound there we looked at a few other molecules and one of them if you remember is phosphoenolpyruvate, because hydrolysis of this ester bond leads to a alcohol group. So it will be, this will be an alcohol and this will be enol. Therefore, this double bond and the OH together we call enol. And it can undergo tautomerization to form ketoenol tautomerization.

So that is sort of resonance kind of stabilization. Therefore, the hydrolyzed structure which will be pyruvate is more stable. So therefore, this we call as a high energy compound. And enolase generates this by dehydration of the 3-phosphoglycerate.

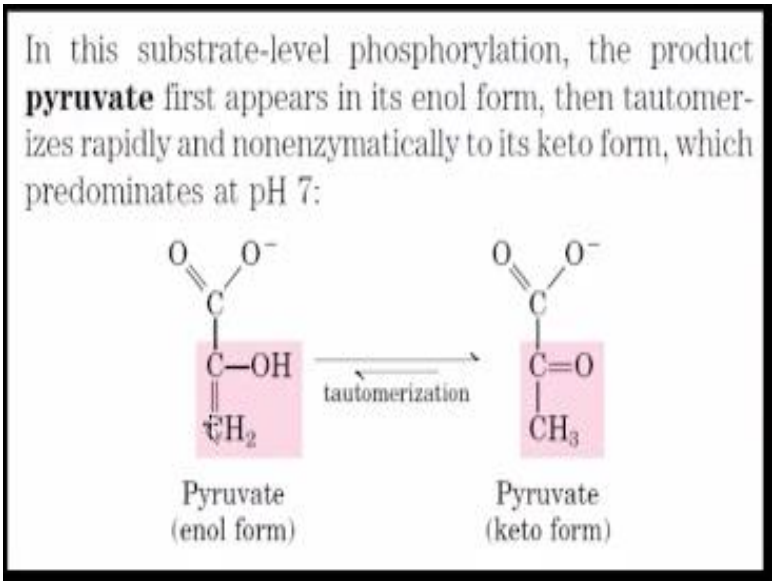
(Refer Slide Time: 12:44)



So the last step is that the hydrolysis of the high energy bond. So you have another substrate level phosphorylation producing ATP molecules. So these two ATP, so so far we have canceled whatever generated and whatever consumed and these two ATPs like one ATP per phosphoenolpyruvate and two phosphoenolpyruvate per glucose, in that sense per glucose two ATP.

So this is the net gain from glycolysis apart from the two NADH produced. In terms of ATP production two ATP molecules are produced per glucose in glycolysis. So this structure produced pyruvate can be in keto-enol tautomerization and due to that, that is more stable.

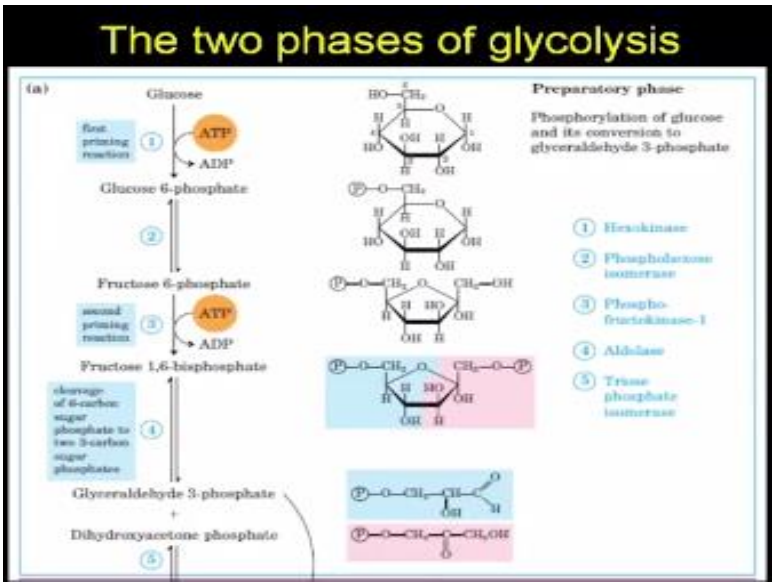
(Refer Slide Time: 13:40)



So that is shown here. So this is the pyruvate in the enol form and this is the keto form, okay. So this is the carbonyl group, we call this the keto group, and this is the enol. So because this is an ene, alkane, alkene, so that ene double bond and here you have the alcohol group, that is where ol comes from. So that is why it is called enol. And this kind of an acid is called alpha-keto acid.

In the old convention, this is not named and this is alpha, beta and so on. As per IUPAC, this will be 1, 2, 3. So this you can call it as 2 keto or alpha-keto acid, okay. So this is how the pyruvate is produced.

(Refer Slide Time: 14:31)



So these are the 10 steps. And this slide sort of tries to, you know, provide us an overall view in terms of summarizing glycolysis. So if you look at it so the first step

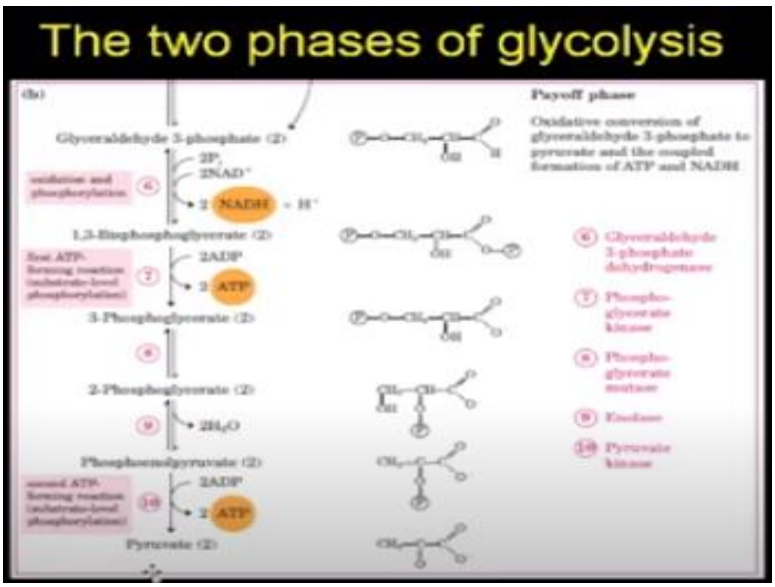
and the third step and then the cleavage into the trioses, so these are the preparative phase, okay during which the compound the reactants are energized and activated for the energy yielding phase.

And the respective enzymes are listed here, we have already gone through it. This is just to give you a snapshot of the, you know the reactants and products and the enzymes whether the reaction is reversible or irreversible. See, look at the first one. This is an irreversible reaction. Third one, it is irreversible reaction. So this catabolic reaction therefore, is favorable only in the degradative direction, okay.

And anabolic thing therefore, we have to have an alternative way of converting fructose 1,6-bisphosphate to fructose 6-phosphate as well as glucose 6-phosphate to glucose. It is not going to be the same enzyme like you know aldolase is not going to sorry third phosphofructokinase is not going to do this reversible reaction. Similarly, hexokinase is not going to do this reversible reaction.

So this is how anabolism and catabolism are separately controlled and therefore, they do not run into a futile cycle. So remember these concepts we learned at the beginning.

(Refer Slide Time: 16:27)



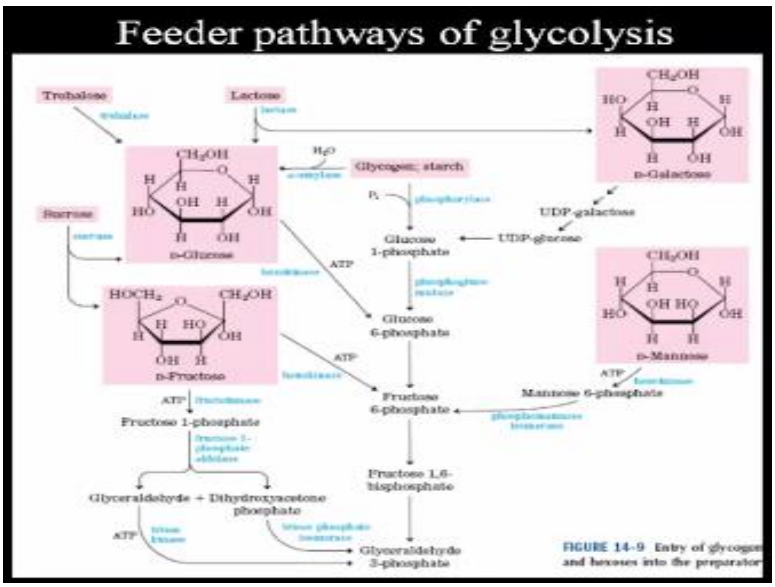
And this is the payoff phase meaning energy yielding phase where we see this aldehyde group oxidation, that oxidation energy is used to reduce NAD to NADH as well as to generate this high energy compound by making a mixed anhydride

structure. And that during hydrolysis you generate producing two ATP and so that is one payoff. Then you have the second payoff at this phosphoenolpyruvate to pyruvate.

And the respective enzymes are shown here again. So here if you see there are two steps again that are irreversible like step 7 as well as step 10. So this is why it is not pyruvate is not automatically going to become glucose. Like for example, if you take alanine, amino acid and remove amino group from it, it will become pyruvate.

And that pyruvate, so the, if you are trying to make glucose from alanine, the first step is to get the amino group out and that usually happens by a reaction called transamination. We will learn that in detail later. And that pyruvate is not readily going to become glucose. It needs enzymes to bypass this catabolic direction of glycolysis.

(Refer Slide Time: 18:03)



Alright, so this sort of summarizes the various molecules from which you get the glycolytic intermediate, okay. So you know, all this will help you as a general knowledge as well. For example, people do not readily understand the difference between eating fatty food versus carbohydrates that is sugar rich food, they do not realize they are all one and the same, okay.

And that is primarily because they all get converted to the same intermediates. Remember, catabolism is convergent, that also we learned initially. So here you see

lactose coming from milk. It is a disaccharide hydrolyzed and you get glucose and the other galactose gets isomerized to glucose again and you know how glucose can enter into glycolysis, glucose 6-phosphate.

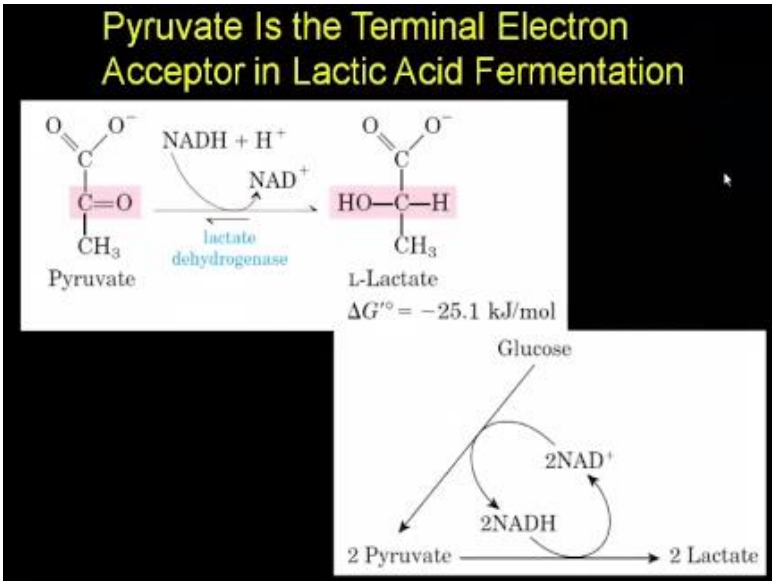
Trehalose, this is usually from fungi. There again it is a disaccharide, hydrolyze the glycosidic bond and isomerize the other one into glucose, then that glucose can enter. So lactose can get to glycolysis, trehalose can get. Similarly sugar that you eat left and right in terms of confectionery, chocolates and other sweets and the sugar you add to milk, coffee, tea etc. That again is a disaccharide.

When you hydrolyze and isomerize the fructose into glucose then you can get this or that fructose can get phosphorylated and then it can straight get into fructose 6-phosphate and get into the glycolytic reaction, okay. And there is one more, fructose 6-phosphate and then that directly becomes fructose 1,6. So this aldolase can cleave into glyceraldehyde and dihydroxyacetone phosphate.

And this isomerizes and then enters again into glycolysis depending on which enzyme is present. You know, hexokinase reaction, fructokinase reaction. And so the other one galactose, if it does not isomerize into glucose then it can actually go via this route and then enter here. And another sugar mannose-6-carbon, that also can enter.

So like this multiple sources of carbohydrates, they can all finally get converted into intermediates of glycolysis. And these steps are what we call as the feeder pathways of glycolysis.

(Refer Slide Time: 20:47)



So now we are going to look at what actually happens to pyruvate, okay. So from glucose to pyruvate, we have some oxidation. So an easy way of finding out the oxidation state of all carbons in a molecule is simply look at the hydrogen carbon ratio. So if you look at it, here compared to glucose, here you have less hydrogen, meaning along with the proton electrons also lost, meaning it is oxidized.

So pyruvate is oxidized compared to glucose. But it is still less oxidized compared to carbohydrate, meaning we can still lose the electrons from it and generate more energy. So we are going to start with this pyruvate and then look at what are the things that can happen to pyruvate. One of them is immediate reduction to lactate okay, lactic acid. This is what happens in your muscle cells when you go for a fast running like sprint, a short sprint.

So that time the oxygen transported from lungs to the muscle cells is not, the rate of transfer does not provide sufficient oxygen for complete oxidation to carbon dioxide. So as a result, the muscle that is requiring energy in a higher rate because you are running fast generates by quickly you know partially oxidizing glucose in the absence of oxygen into lactic acid.

So the glucose entering into glycolysis comes to pyruvate and as end of pyruvate, this sorry end of glycolysis pyruvate gets reduced to lactic acid. And this reduction uses the NADH and in that process NADH gets oxidized, okay. So remember, at the earlier

step that is glyceraldehyde 3-phosphate dehydrogenation to produce 1,3-bisphosphoglycerate there be generated NADH.

And if this NADH is not produced through oxidative phosphorylation or other means, then glycolysis cannot continue because the cell will run out of oxidized form of NAD. And this lactate dehydrogenase step regenerates that. So that is summarized here. So glucose to pyruvate you end up reducing NAD. So this is what is happening at the glyceraldehyde 3-phosphate dehydrogenase step.

And that reduced one, the four electrons that are here, if it goes to electron transport chain, that is when oxygen is available in mitochondria this can be used to generate proton gradient. But in the absence of oxygen for continuous breakdown of glucose, because glucose to pyruvate you will still get 2 ATP and that 2 ATP could be useful to provide the energy for you to run. And that ATP to generate you need continuous availability of this NAD.

And that is generated by converting pyruvate to lactate. So in this process NAD is consumed. And therefore, this oxidize further oxidizing, replenishes NAD required for the glyceraldehyde 3-phosphate dehydrogenase step. And in that sense, or this becomes very crucial for anaerobic production of ATP from glucose. This is what our muscle cells do. But this cannot go continuously.

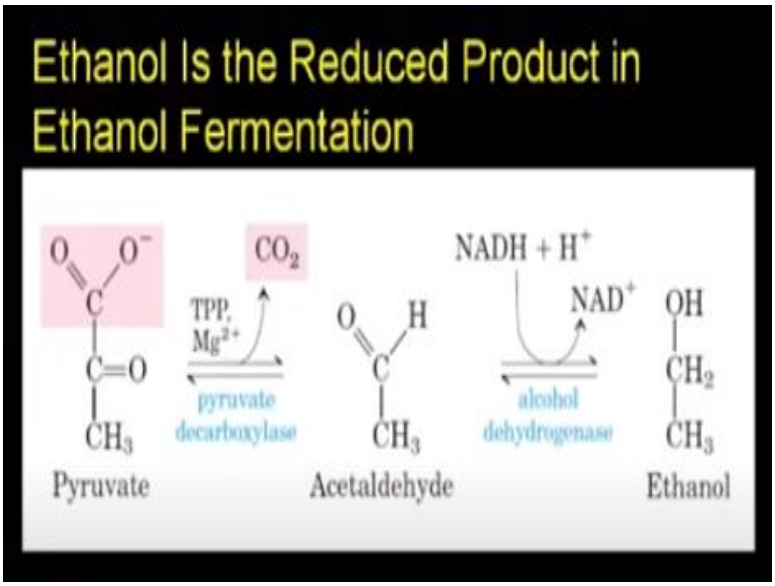
You could have you know, drunk lot of sugary syrup and you could be running and you do not care inefficient production of ATP, because you can produce lot of glucose and therefore, even at two ATP per glucose, you can really make lot of ATP. But the problem is the lactic acid is going to reduce the pH and due to that you will have problems. So as a result of acidification of muscle cells, you cannot really run too fast for long.

Maximum, one minute you can sustain the very high speed running. And beyond that, you will have muscle cramps due to pH reduction. And this lactic acid if you count the carbon hydrogen ratio is the same as glucose, okay. So the oxidation state is not changed, the energy is still conserved here, except that you gain two ATP molecules per glucose. So this is one fate of pyruvate.

That is pyruvate can be reduced by lactate dehydrogenase to make lactic acid. And this lactic acid in during the recovery period is transported back via bladder to liver where the liver will use this lactate to make glucose again. And that glucose can go back to muscle to feed into glycolysis to come all the way to pyruvate. In the process, you will generate a two ATP molecules.

So that is the relationship between muscle and liver during that kind of active exercise. So this sort of a process where you do not require or you do not use oxygen, but derive energy out of carbohydrates and that is the definition of fermentation, okay. So fermentation is abstraction of energy from carbohydrates without using oxygen. So that is the biochemical definition of fermentation.

(Refer Slide Time: 27:06)



So in yeast on the other hand unlike our muscle cells, the yeast has an interesting additional enzyme which we do not have is the pyruvate decarboxylase. This pyruvate decarboxylase will it will remove this carbon dioxide from pyruvate, produce acetaldehyde, which in the presence of alcohol dehydrogenase, remember this enzyme we have encountered in as an example of competitive inhibition while studying enzyme inhibitions, okay.

Using alcohol dehydrogenase just like lactic acid here again the same, the reduced NADH is oxidized and that is used to reduce acetaldehyde to ethanol. Again ethanol like lactic acid has the same hydrogen carbon ratio as glucose. So therefore, the

oxidation state of the molecule is not changed, but then you have gained that two ATP at the phosphoenolpyruvate to pyruvate step; that two ATP is still net gain.

So this is alcohol fermentation. An interesting aspect of this two enzyme step is the production of carbon dioxide and that is why beer, champagne etc., have bubbling property. That is coming from this carbon dioxide produced during alcohol fermentation by yeast. And this carbon dioxide is the reason for the natural carbonation of beer and champagne, okay.

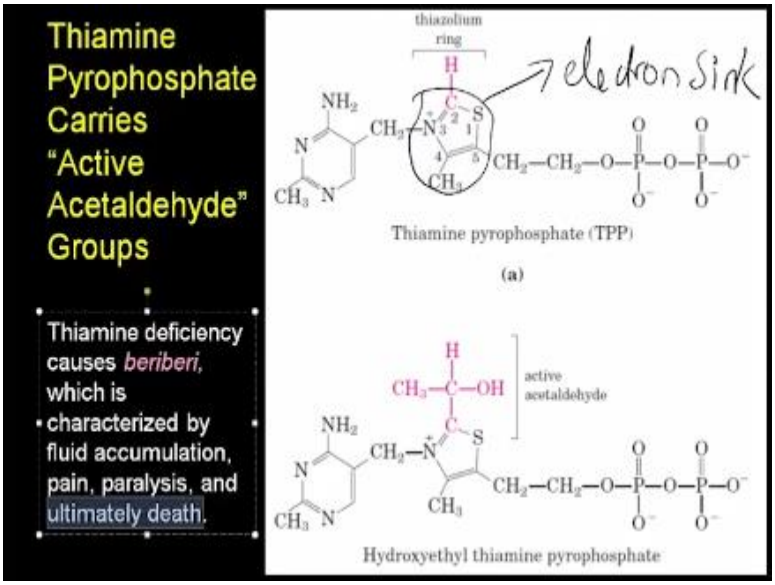
And the other very important point I want to draw your attention to our third B complex vitamin enters into the picture which is thiamine, okay. So we have learnt nicotinamide adenine dinucleotide where the vitamin B complex vitamin niacin we encountered, okay. Niacin is part of NAD and we know NAD is an important intermediate electron carrier.

And then we saw another one riboflavin that is the vitamin B, which is part of the FMN and FAD, flavin mononucleotide and flavin adenine dinucleotide. And this is the third vitamin, thiamine. Now this thiamine is important cofactor for enzymes involved in or decarboxylation as you see in this example or where acetaldehyde group may split temporarily transferred from one substrate to another one.

So these are the two steps in which this thiamine becomes important. So therefore, we will spend a couple of minutes on TPP and then we will move forward with pyruvate. So, so far we have seen two things about pyruvate. One, pyruvate can become lactic acid and thereby regenerate the oxidized NADH required for (()) (30:17) step in glycolysis.

Second in yeast due to the action of pyruvate decarboxylase pyruvate can become ethanol via acetaldehyde. So this is the alcohol fermentation, where glucose is fermented to ethanol in the absence of oxygen.

(Refer Slide Time: 30:40)



Okay, so now to look at the beauty of thiamine pyrophosphate structure. So what we need to do is we need to focus on this ring. So this is the thiazolium ring. So this carbon 2 is acidic, which you know due to the electron deficient structure of this ring and that readily dissociates a proton and forms a carbanion. And that carbanion as we have learnt very early will very readily react with a carbonyl carbon, okay.

Because carbonyl carbon is positively charged and then carbanion will be negatively charged. So and which results in and that usually results from a cleavage when this carbanion reacts with a carbonyl carbon and you have a carbon-carbon bond cleavage in the molecule in which the carbonyl is present, carbonyl group is present. And that leads to a carbanion generation, which is highly reactive and unstable.

And that is usually stabilized by the formation of this acetaldehyde structure here where that additional electron is delocalized through resonance in this ring structure. And this is a common recurrent theme in biochemistry like where you have a ring structure which is electron deficient, which can temporarily delocalize electrons through resonance formation among these double bonded ring structure, okay.

And that theme will reoccur again and again and such ring structures we call as electron sink, okay. So I am sure you may have learnt this in you know, chemistry somewhere, but I just want to refresh your memory. So these are called the electron sinks okay, this kind of a structure, that is an electron sink. So we will see this in an actual reaction.

We will look at the pyruvate decarboxylase reaction mechanism and there we will get a clear idea of this. So this is a very crucial thing. So the thiamine pyrophosphate, here we are seeing with pyruvate decarboxylase as example, and I said this enzyme is present in yeast and not present in us. And therefore I do not care about, do not think that way, or this vitamin may not be important for us.

There are numerous decarboxylation steps in our body as well as there are many situations where acetaldehyde group transfer is important. Due to this TPP is extremely important, okay. So you will see a reaction later, not in today's class where we are going to proceed from pyruvate to the oxidative phosphorylation step where the oxidative phosphorylation and pyruvate is linked by a cyclical metabolic pathway called citric acid cycle or Krebs cycle.

At the junction between glycolysis and that TCA cycle or tricarboxylic acid because you have three carboxyls in one molecule there and in that between the two is pyruvate to acetyl-CoA formation and there you need TPP again. So this is extremely crucial and due to that thiamine deficiency can be fatal, okay. It can ultimately lead to death. So thiamine deficiency causes beriberi.

Remember niacin is pellagra. So we saw rickets with respect to vitamin D. That is a lipid soluble vitamin. So beriberi leads to is characterized by fluid accumulation, pain, paralysis and ultimately death. So these are important vitamin. So usually we do not suffer vitamin B deficiency primarily because most of the food that we eat you know in some or the other, you get vitamins, the B complex vitamins.

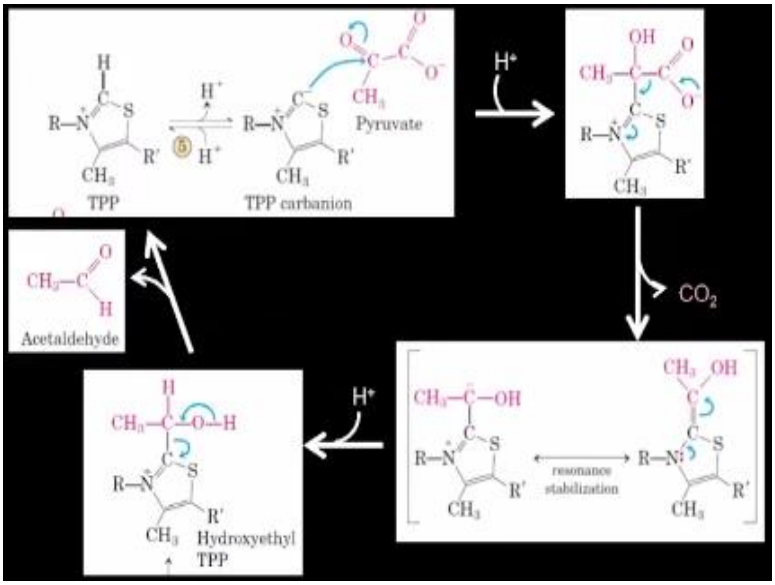
These are water soluble vitamins. They are readily excreted. And as a result, hyper vitamin based diseases do not happen. That is called hypervitaminosis. That is not associated with B complex. And B complex vitamins are available from variety of plant sourced food and that is one of the reasons why you need to eat a variety of vegetables in your diet you know at some time or the other.

So having variety in the food is one of the reasons for to fulfill the requirements or dietary requirements of all these vitamins. So normally you do not run a deficiency of

these vitamins but in malnutrition conditions that can happen and that is how we are aware of a disease like beriberi. So in India malnutrition is still common. So therefore, vitamin deficiency is still a problem.

So I cannot you know undermine the importance of this. Okay, let us get to the reaction mechanism of pyruvate decarboxylase.

(Refer Slide Time: 36:46)



So in school you may have memorized vitamins are important. So now you are actually seeing where the vitamins actually function. So this is the thiazolium ring. So where this is little acidic carbon which can readily dissociate this proton and become carbanion. And we have already learned at the very beginning even before we got into metabolism that these carbanions can readily you know, attack a carbonyl carbon because this is an electrophile and this is a nucleophile, okay.

And that leads to the formation of this intermediate. So here you have this see this is the ethyl group, two carbons and once you remove this by decarboxylation, so this will be an ethyl group. So this is a hydroxy ethyl. Okay, when you have another hydrogen for this as you see here. So because this can readily delocalize electrons that favors this decarboxylation and then you get this structure.

And this structure because of the delocalization of electrons, this is the resonance stabilization between the two forms. So you have either this double bond or the carbanion. And both of this can readily be stabilized by delocalization with among

these atoms, among these bonds, okay. And then protonation leads to the formation of this hydroxyl ethyl structure.

So this is how acetaldehyde is carried and therefore this hydroxyethyl structure is normally called active acetaldehyde group, okay. So this is actually activated form which can readily react meaning here readily donate the acetaldehyde to another substrate. So that is the kind of reactions in which TPP becomes important. So when we learnt about the type of reaction, so first I learnt about oxidation reduction reaction.

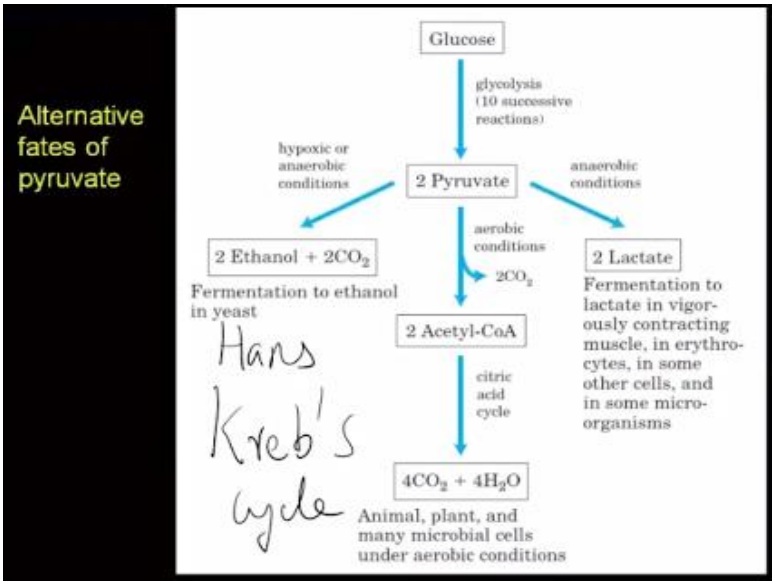
Second, we talked about carbon-carbon bond formation or breakage. There we saw the importance of carbonyl carbon and we learnt about aldol condensation, glycine condensation and the third was alpha-keto acid decarboxylation. And that is the example here you are seeing, okay. So here, carbanion and you have the carbonyl carbon, the partially positive carbon.

And that results in decarboxylation of this alpha-keto acids. This is the alpha carbon, so we do not count this. In IUPAC this is 1 and 2. So pyruvate would be 2-keto acid or alpha-keto acid. So the alpha-keto acids carbonyl group is the one that favors the decarboxylation of such acids. Now here you will see an example of that.

And then so again the rearrangement of electrons here generates acetaldehyde and produces TPP that by taking proton sorry losing a proton into the media generates this active carbon ion, okay. So these are the five steps of the TPP based decarboxylation of pyruvate decarboxylation. So this is an important enzyme reaction mechanism.

Make sure you go through this multiple times. The main point is this, this carbon ion and carbonyl carbon reaction.

(Refer Slide Time: 40:57)



Okay so, so far we have seen glucose to pyruvate to lactic acid as well as pyruvate to ethanol, okay. So a third fate of pyruvate happens when you have plenty of oxygen available which is the normal situation in all our cells. There the pyruvate gets oxidized to carbon dioxide. Remember in terms of the oxidation states of carbon dioxide, this is the most oxidized stage.

So this happens when oxygen is plenty and that is aerobic conditions during which pyruvate gets converted to acetyl-CoA which enters into a cyclical biochemical pathway called citric acid cycle because one of the intermediates of the pathway is citric acid.

Citric acid has three carboxyl groups and therefore it is also called tricarboxylic acid cycle or in memory of the or in honor of the scientist who discovered this pathway it is called Krebs cycle okay, Krebs cycle. So Hans Krebs is the scientist who discovered this pathway. So our next goal will be that. So we will learn about TCA cycle. But before that, we have to do a few small you know finishing up of the glycolysis.

One of them is glycolysis regulation itself. You know glycolysis is an interesting pathway that is the central as I told you at the beginning to metabolism in all organisms, it is subject to regulation. And one of the main point is in the absence of oxygen glycolysis is the main source of energy, okay. So for example, if you take a cancer tissue, you know a tumor that is growing.

Initially when the tumor starts to form as it enlarges, it will not have induced blood vessels to supply blood to the inner parts of the tumor. Due to that, it will not have plenty of oxygen available. So the oxygen in our tissues is primarily from the blood and oxygen in the blood is from the lungs, okay. So lungs is where, from the atmospheric air you have the oxygen loaded onto hemoglobin.

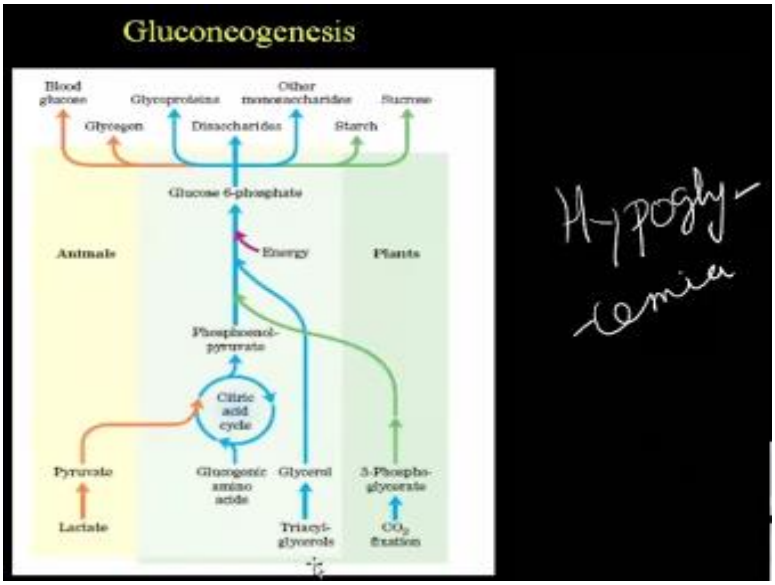
And hemoglobin in the blood takes the oxygen to tissues. Now if a tissue does not have blood vessels nicely supplied then it is not going to have oxygen. So to draw enough oxygen and other nutrients, cancer tissues the tumors induce blood vessel formation, a process called angiogenesis. But when they are still in the process of inducing and the angiogenesis and the blood vessels have not yet formed, the middle of the tumor will not have enough oxygen supply.

So due to that, they rely on glycolysis to get enough energy for the cell proliferation. And due to this, tumors are highly active in glycolysis. And this process was originally identified that tumor cells have higher rate of glycolysis then other tissues or the normal tissues was identified by a scientist by name Otto Warburg, okay. And due to that it is called Warburg effect. Okay, so this tumor having high glycolysis.

And even before him Louis Pasteur growing yeast and other microorganisms realized in the absence of oxygen in anaerobic conditions, glucose breakdown was happening at a higher rate. And that is because glycolysis is the primary way of getting the required ATP molecules, which means you need to break down lot of glucose.

And due to that glucose uptake by the microorganisms in the absence of oxygen was high. And that is called Pasteur effect, okay. So Pasteur effect is higher glycolysis in microorganisms in the absence of oxygen, that is anaerobic conditions. So this was observed by Pasteur and that is called Pasteur effect. Then Warburg discovered the same thing in tumor, and that we call as Warburg effect, okay. So remember those things. That is about the regulation of glycolysis.

(Refer Slide Time: 46:18)



So next what we are going to do is we are going to look at the reverse of the whole thing to make glucose. So why would you make glucose? You know glucose is not directly currency of energy, and I need it to oxidize glucose to make ATP. And we saw through the feeder pathways, many other molecules can actually be converted to intermediates of the glycolysis. And we can get energy from them as well.

If that is the case, why would I ever need to make glucose? That is because other molecules do not readily cross the blood brain barrier. And brain depends on availability of glucose for all its energy needs. And among the organs in our body, the one that requires the maximum energy is our brain. So that is why if the blood glucose level goes below a certain level, you get into coma, okay.

And that is called hypoglycemia. So you cannot have hypoglycemia, you will immediately get into coma. So you would think too much glucose is always bad, because that is what is diabetes all about. But the opposite is also sorry the opposite is also true. That is primarily because of the way our brain uses, you know depends on this. So hypoglycemia, again is a serious condition.

Like this is lowering of glucose in blood. And due to that brain will not have sufficient energy and due to that its activity will go down and then you will get into coma. To avoid that glucose production is important. Maintenance of the normal levels of glucose, like about roughly about 70 milligrams per 100 ml of blood is really crucial. If it goes below 40 you will go into coma.

So therefore how do we make glucose from other things, suppose you know glucose is not readily available, and that is the reason you will not have glucose in the blood. So there are variety of ways. So I will complete that and then stop. So lactate is one source. Lactate produced in the muscle comes to liver and liver converts lactate to pyruvate by the reversal of the lactate dehydrogenase step that we saw already.

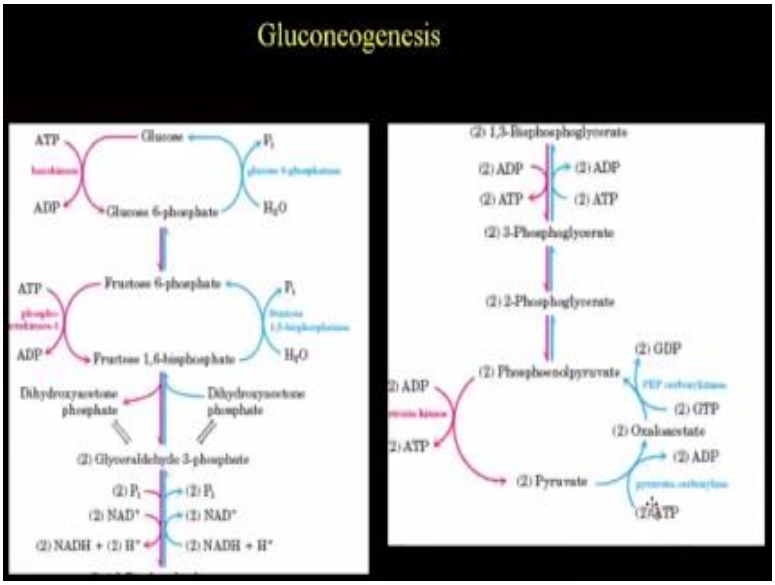
And this pyruvate can get into citric acid cycle and then go back to glucose. So pyruvate citric acid connection, I will tell you in the next class. So this is one route. The other one is triacylglycerols, you know the fatty acids in acyl form ester bond with the glycerol. So they can be hydrolyzed and this glycerol can become glyceraldehyde 3-phosphate and enter into glycolysis and go back.

And free fatty acids also can go, that let us not worry for now. Then plants and some microbes like cyanobacteria, they can fix carbon dioxide using sun's energy and produce 3-phosphoglycerate which can also get into glycolytic intermediate and go back to make glucose which can go into making all of this like an important thing in hypoglycemia is blood glucose.

Suppose you are eating only meat and never eat any carbohydrate food, then you are depending on amino acids for producing blood glucose, okay. So there are like for example alanine transamination can generate pyruvate and that can go into forming blood glucose. Excess of glucose produced even that way can become glycogen in liver. And glycoproteins we know what they are and what is their use.

Disaccharides like lactic acid sorry lactose in mammary gland or sucrose, maltose, all of that other monosaccharides. And in plants of course, starch and sucrose. So this sort of reversal is what is gluconeogenesis, okay.

(Refer Slide Time: 51:03)



So in the next class, we will look at the I will just briefly show you, so this is the glycolysis that we already saw, glucose to pyruvate, which is marked in the pink color here. And I told you the reversal cannot happen by identical enzymes. So what are the steps, the bubble like structures; that we will focus in detailed way tomorrow. Okay, so I will stop here.